Radiation Hormesis

Beneficial Effects of Low-Dose Radiation

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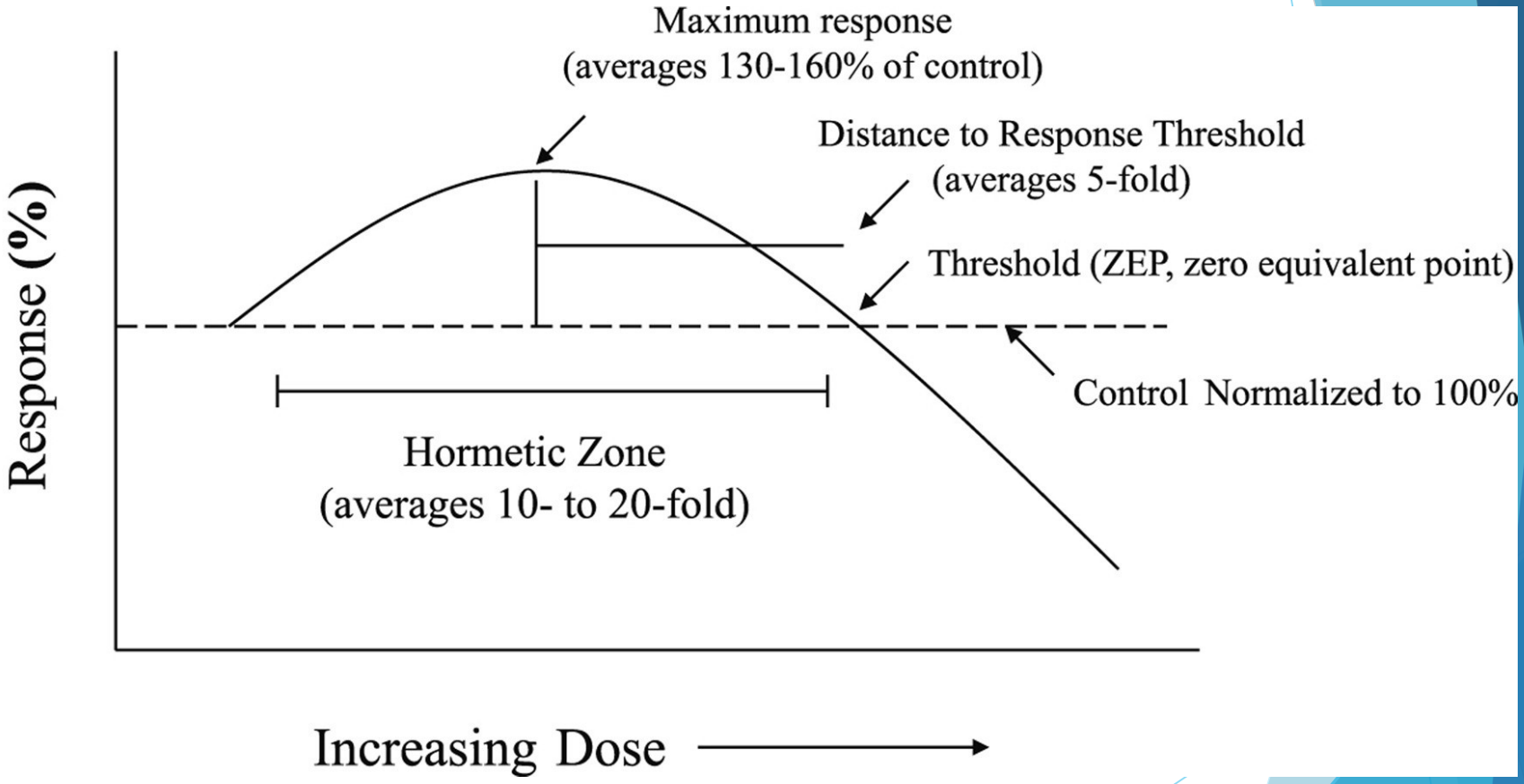
What is Hormesis?

Hormesis – an innate capacity that enhances survival and biological performance across wide range of activities via *upregulation of adaptive response mechanisms* following exposure to low levels of harmful stressor agents

Calabrese, E.J. and Agathokleous, E., *Hormesis: Transforming Disciplines That Rely on the Dose Response*, IUBMB Life, June 28, 2021

Generalized Hormesis Curve



Calabrese, EJ and Giordano, J, *Ultra low doses and biological amplification: Approaching Avogadro's number*, Pharmacological Research, Vol. 170, August 2021

Reality of Hormesis[a]

Humans and all other mammals have forever been exposed to ionizing radiation throughout life, yet have not perished due to adaptation to prolonged genomic stresses *(genomic stress adaptation)*

- Low radiation doses associated with natural background radiation exposure help maintain life by enhancing body's natural protection mechanisms against cancer
- Low-dose enhancement is *consequence of genomic stress adaptation* - without this adaptation highly unlikely that humans and other mammals would exist today given all genomic stresses encountered throughout life

Adaptive Response Mechanisms[a]

- At least 6 different low-dose and low-dose-rate radiation adaptive response mechanisms account for lower cancer rates and greater longevity in humans
- *Stimulation of adaptive response mechanisms* by low radiation doses repair more than 99.9% of DNA damage
- Adaptive response mechanisms include:
  - enhanced production of antioxidant enzymes[6]
  - enhanced production of DNA repair enzymes[5]

Adaptive Response Mechanisms (cont.)

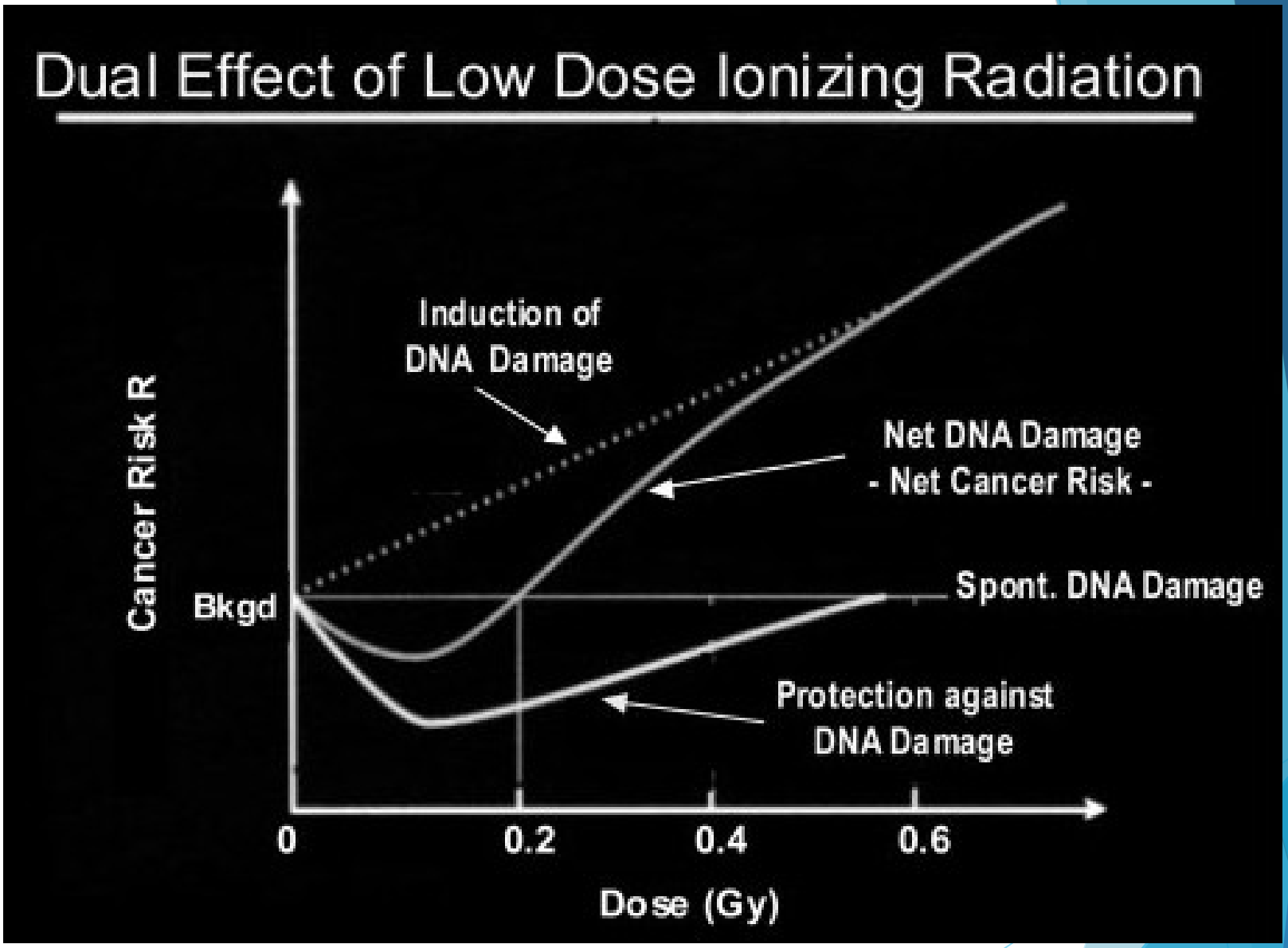
- Response mechanisms (cont.):
  - slowed mitosis (permits DNA repair enzymes to accomplish their function)[6]
  - induced apoptosis (destroys unrepaired cells)
  - bystander effects (neighboring undamaged cells trade chemical messengers to enhance apoptosis in cells with unrepaired DNA)
  - enhanced immune system surveillance and removal of remaining unrepaired cells[7]

Radiation Hormesis

- Although large acute doses of ionizing radiation
  can induce cancer, small doses reduce total cancer *mortality* in both animals and humans[1,2,3]
- Concept of radiation hormesis currently applied to physiological effects of acute low Linear Energy Transfer (LET) radiation exposures in range of 1 to 50 cGy (or 50 rads) of total absorbed dose
- Gamma-rays and x-rays constitute low LET radiation, for which 1 cGy = 1 rad = 1 rem

Radiation-induced Adaptive Protection

- Response of body's adaptive protection systems dependent on dose-rate, as well as total dose
- Probability of radiation-induced adaptive protection measurably outweighs probability of damage from acute whole-body doses well below 0.2 Gy of low LET radiation (next slide graphic)[4]



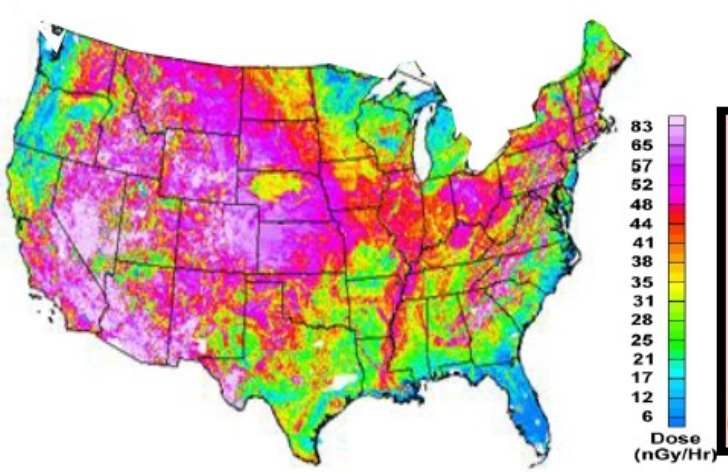
Ref. *Evidence for Beneficial Low Level Radiation Effects and Radiation Hormesis*, L.E. Feinendegen, MD, The British Journal of Radiology, 78 (2005), pp. 3–7

Radiation Exposure and Cancer Mortality Observations

U.S. Radiation Exposure vs. Cancer Mortality

Next two slides show areas of highest gamma-ray and cosmic-ray radiation exposure in U.S. also areas of lowest cancer mortality

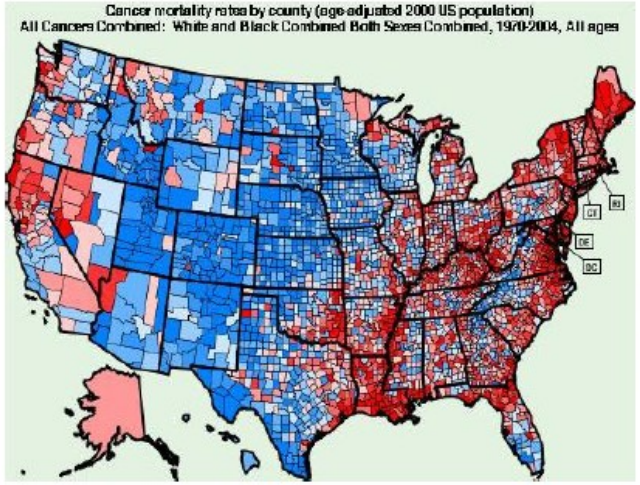
Gamma-Ray Dose vs. Cancer Mortality Rate



Gamma-Ray Absorbed Dose

Duval, J.S., Carson, J.M., Holman, P.B., and Darnley, A.G., 2005, *Terrestrial radioactivity and gamma-ray exposure in the United States and Canada*
U.S. Geological Survey
(0.1 - 0.7 mGy/yr) Open-File Report 2005-1413.

http://pubs.usgs.gov/of/2005/1413/


Cancer mortality rates by county (age-adjusted 2000 US population)
All Cancers Combined: White and Black Combined Both Sexes Combined, 1970-2004, All ages

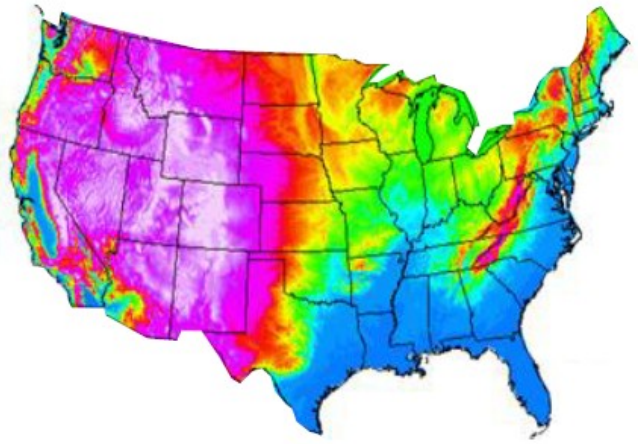
Cancer Mortality Rates by County

All Cancers, etc.…
1970-2004
Deaths per 100,000 person-years

(0 – 325 deaths per 100,000 p-y)

http://ratecalc.cancer.gov/ratecalc/index.jsp

Cosmic-Ray Exposure vs. Cancer Mortality Rate



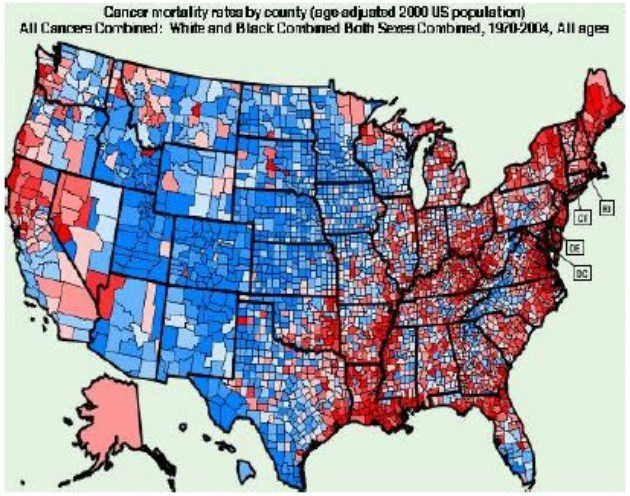
Cosmic-ray Exposure

(calculated from the topography)

U.S. Geological Survey
Open-File Report 2005-1413.

(0.4 - 0.8 mGy/yr)

http://pubs.usgs.gov/of/2005/1413/


Cancer mortality rates by county (age-adjusted 2000 US population)
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Cancer Mortality Rates by County

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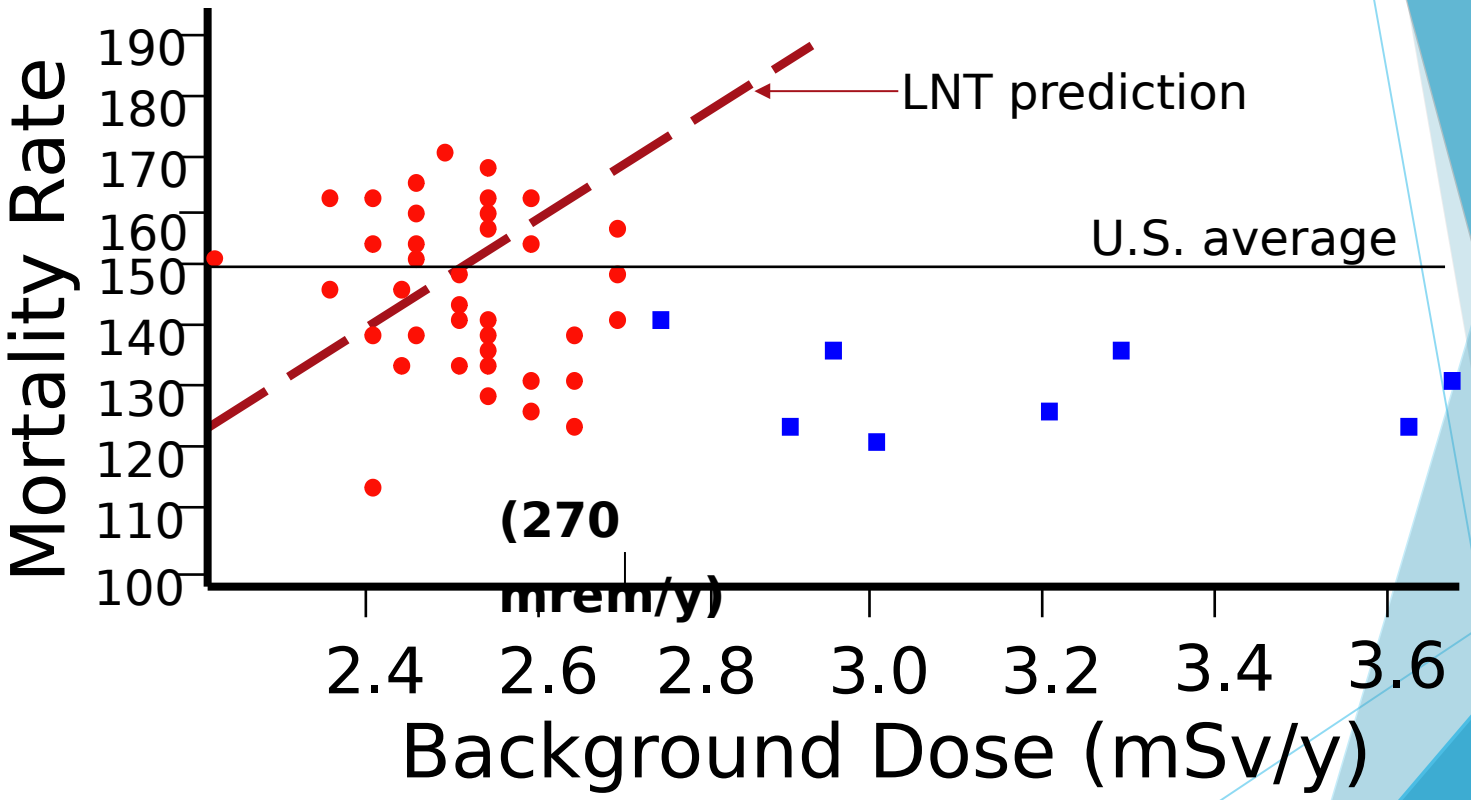
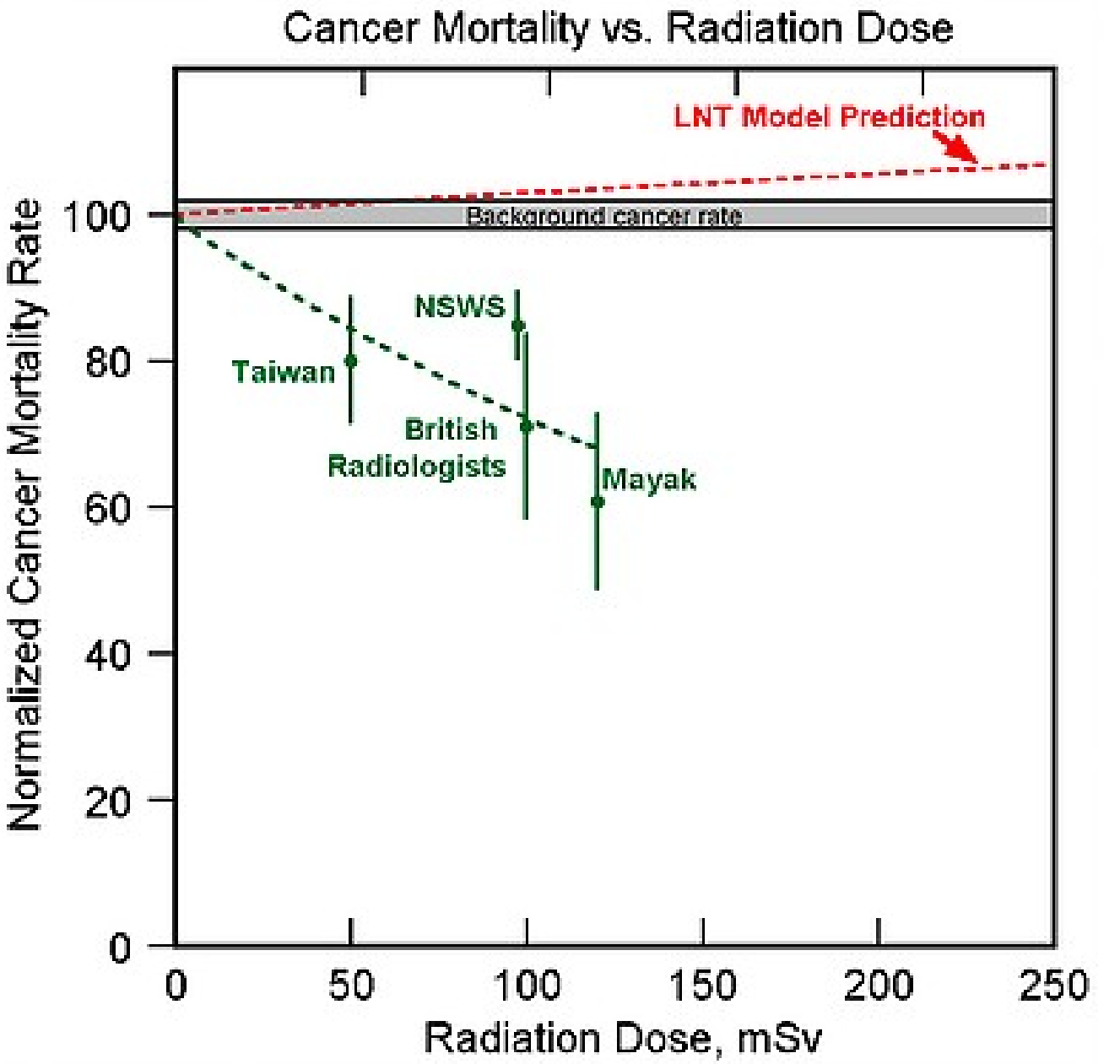
Deaths per 100,000 person-years

(0 – 325 deaths per 100,000 p-y)

http://ratecalc.cancer.gov/ratecalc/index.jsp

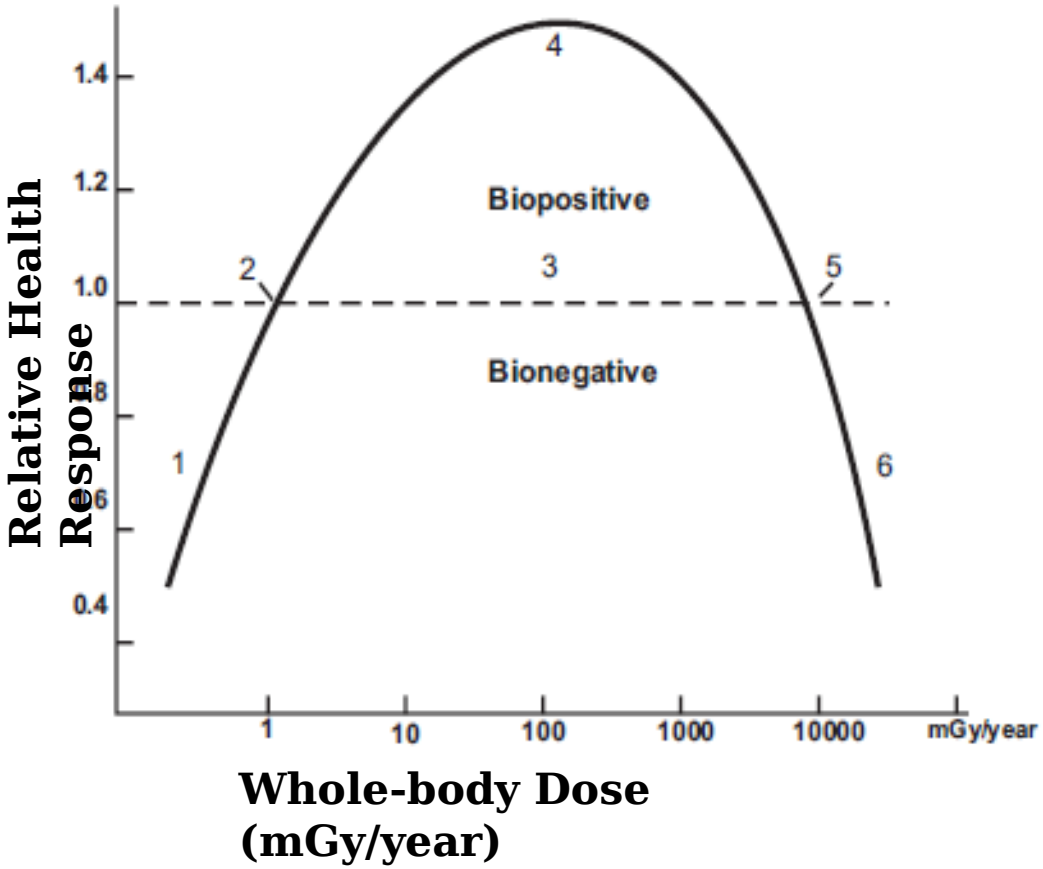
Background Radiation Differences on Annual Cancer Mortality
Rates per 100,000 for 46 U.S. States over a 17-Year Period




Cancer Mortality vs. Radiation Dose
LNT Model Prediction
Background cancer rate
NSWS
Taiwan
British
Radiologists
Mayak
Normalized Cancer Mortality Rate
100
80
60
40
20
0
0
50
100
150
200
250
Radiation Dose, mSv

Idealized Dose Response Curve for Ionizing Radiation

Idealized Dose-Response Curve[25] for Chronic Radiation Exposure



Y-axis approximates responses compared with controls (dashed line – about 1 mGy/yr)

X-axis estimates chronic whole-body doses (1 – deficient region, 2 – ambient dose, 3 – hormetic region, 4 – optimum dose, 5 – zero equivalent point, 6 – harmful region)

Idealized Dose-Response Curve (cont.)

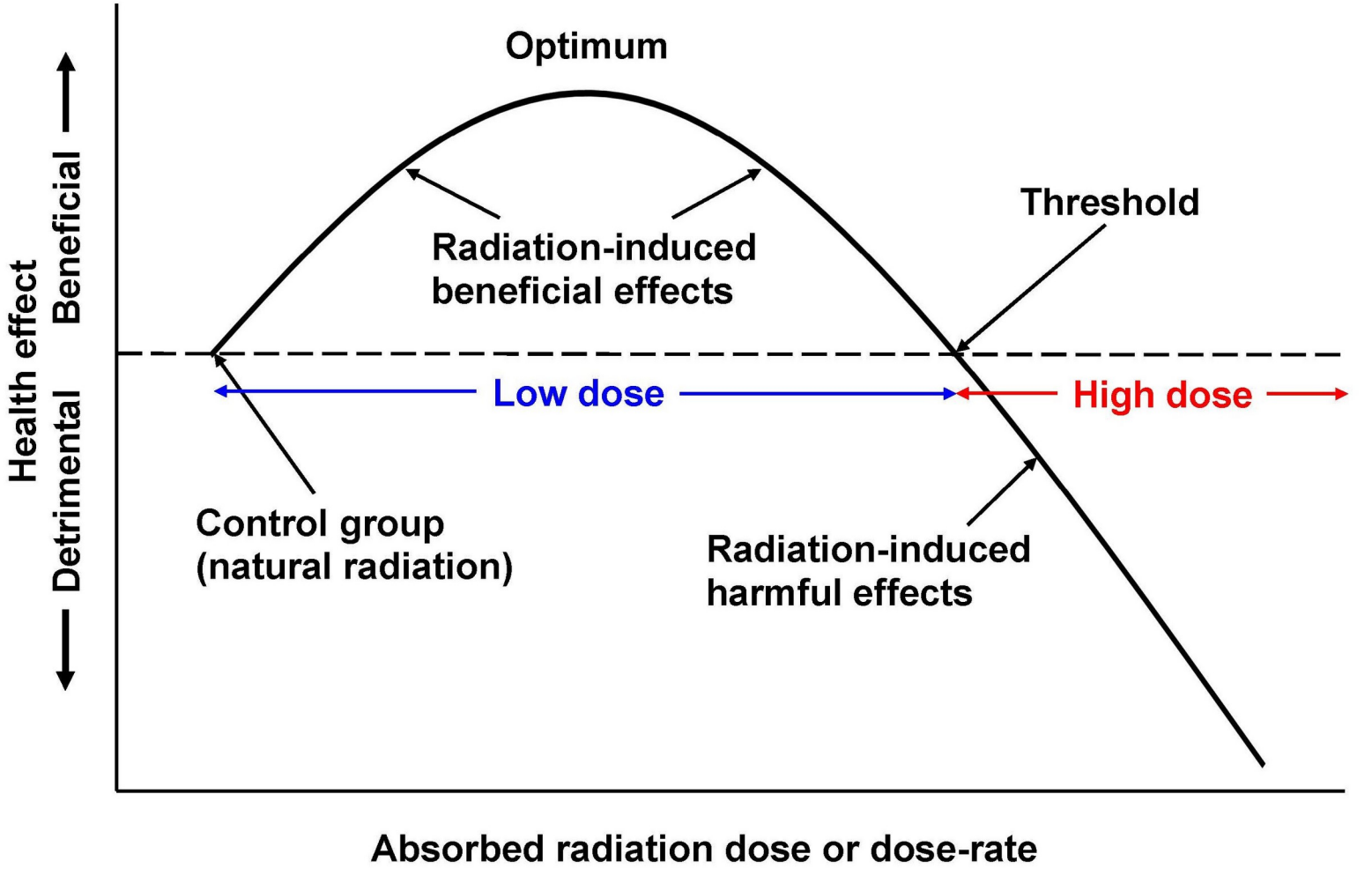
- Dose not cumulative for chronic low-dose/dose-rate ionizing radiation
  - Body's natural defense mechanisms for remediating cell damage not inhibited by low doses of radiation and can repair radiation-induced cell damage in about 24 hours; no long-term accumulation of cell damage
  - More meaningful rate for communicating chronic ionizing radiation exposure would be milli-gray per hour
- Response of body's natural defense mechanisms to low-dose radiation not acknowledged by agencies that regulate radiation exposures
  - Agencies essentially deny validity of data exhibiting beneficial biological effect from low-dose/dose-rate ionizing radiation (biopositive region of dose-response curve)

Idealized Dose-Response Curve (cont.)

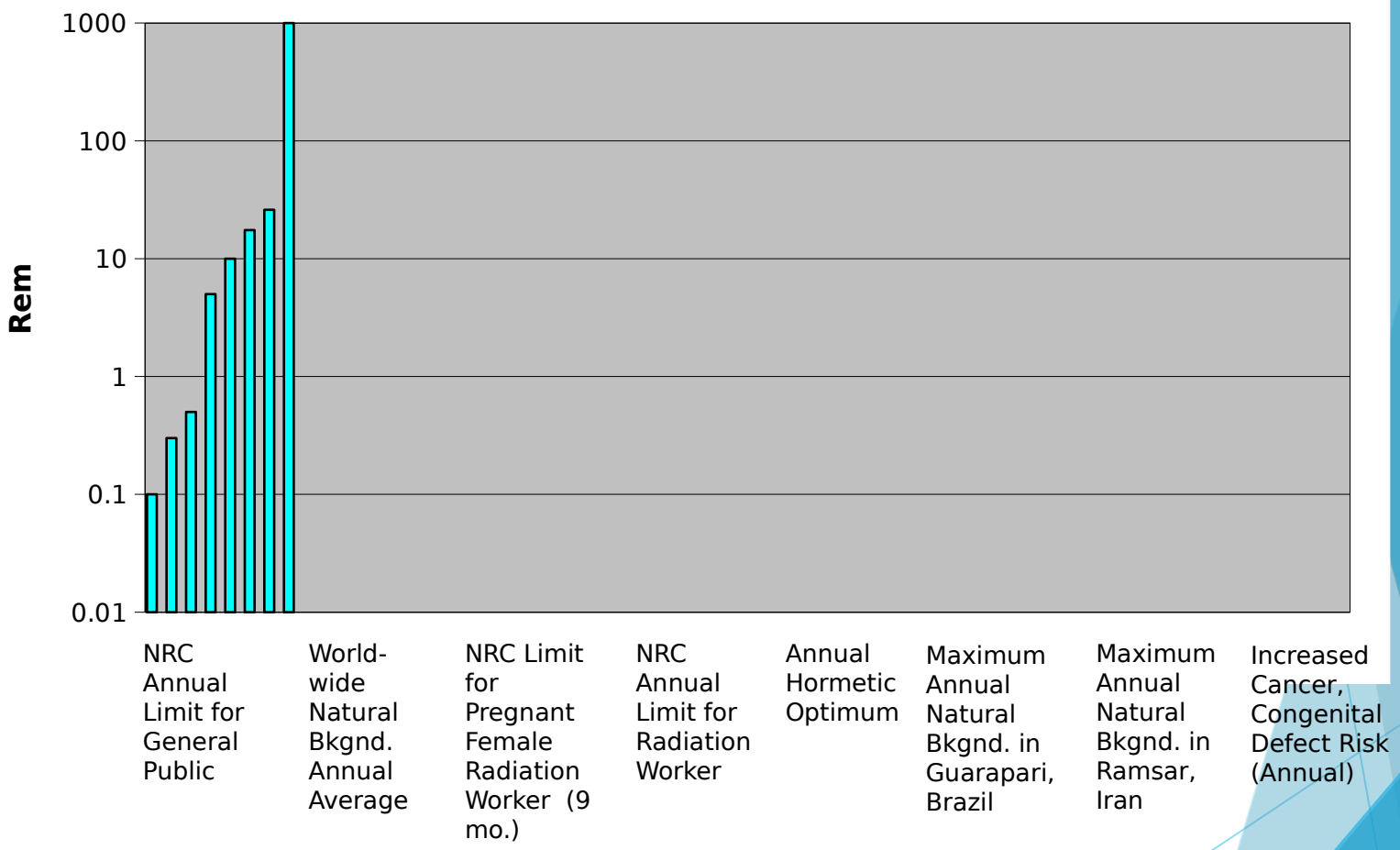
Radiation-induced hormesis more appropriately associated with hourly dose-rate

- Begins to appear at chronic whole-body low dose-rate threshold approximately 0.0001 mGy/hr
- Optimum ionizing chronic radiation dose-rate associated with minimal cancer death rate and maximal life span about 0.01 mGy/hr
- Increased rates of cancer and congenital defects associated with chronic dose-rates >1 mGy/hr

Idealized Dose-Response Curve (cont.)

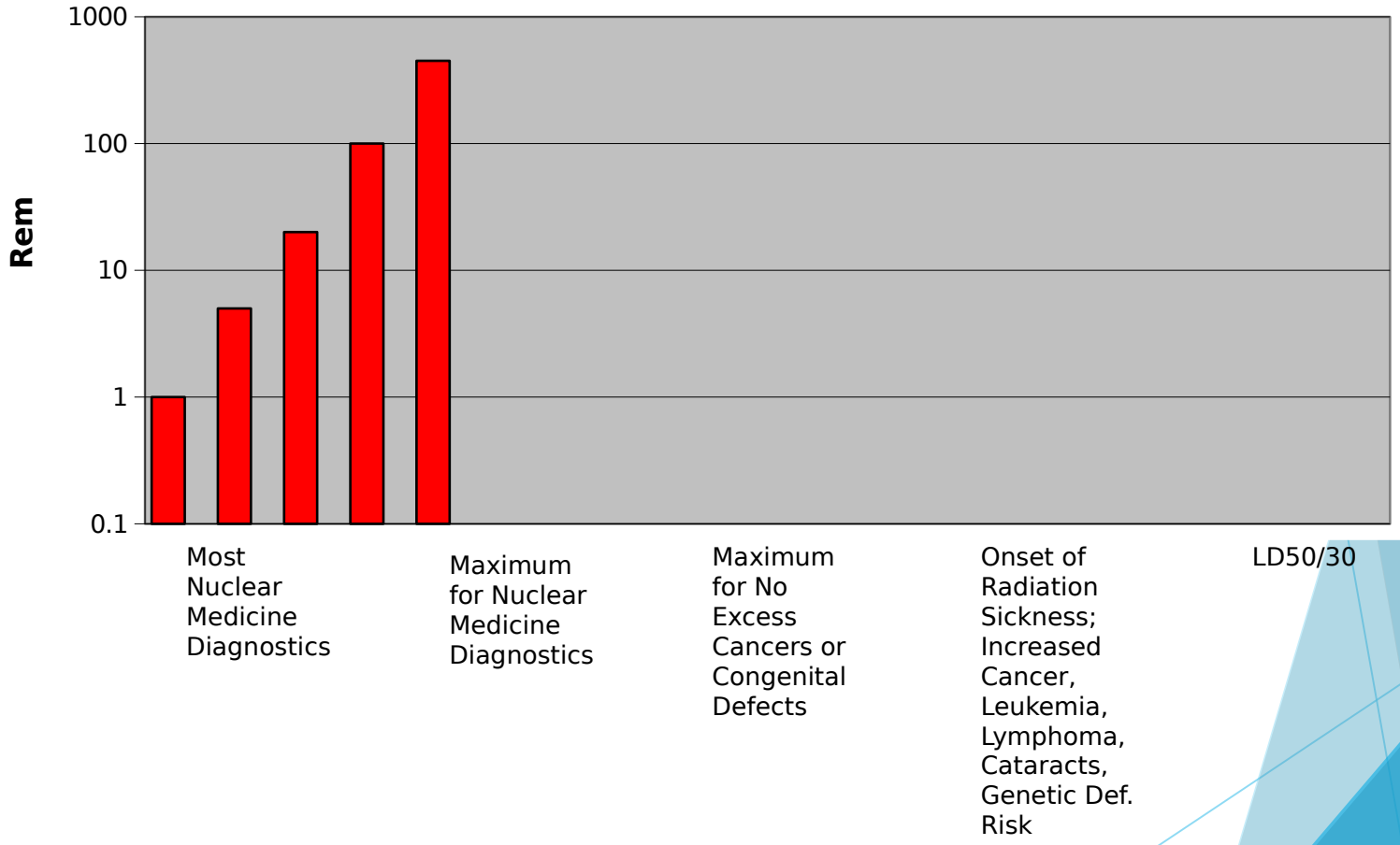


Chronic Radiation Dose Characterization



Body's adaptive protection mechanisms not overwhelmed by chronic low-dose radiation exposures <100 rem per year

Acute Radiation Dose Characterization



Body's adaptive protection mechanisms not overwhelmed by acute radiation doses <20 rem (0.2 Gy)

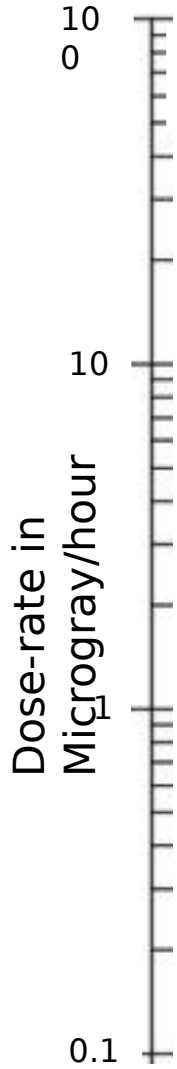
Reasonable Radiation Thresholds Based on Hormesis Data

- Acute whole-body high-dose threshold for increased cancer risk approximately 200 mGy (20 rem)[4]
- Longevity most important health effect of chronic exposure to ionizing radiation
  - Natural background radiation exposure includes both external low-LET radiation (gamma-ray) exposures and internal high-LET radiation (radon) exposures

Reasonable Radiation Thresholds Based on Hormesis Data (cont.)

- Chronic high-dose-rate threshold for reduced lifespan
  - Reasonable low-LET radiation high-dose-rate threshold for reduced lifespan around 700 mGy/year or about 0.08 mGy/hr (80 µGy/hr)[32]
  - Equivalent lung dose-rate of around 30 µSv/hr from high natural background radiation (radon) results in no observable lifespan reduction for residents of Ramsar, Iran (therefore, high-LET radiation absorbed dose-rate of 1.5 µGy reasonable high-dose-rate threshold with potential to result in reduced lifespan)

Chronic Exposures in Perspective



Low-LET High-Dose-Rate Threshold (80 µGy/hr)

U.S. public chronic exposures to internal and external ionizing radiation are well below thresholds for potential lifespan shortening

High-LET (Internal) High-Dose-Rate Threshold (1 µGy/hr)

U.S. average natural background absorbed dose-rates:
Low-LET – 0.12 µGy/hr
High-LET – 0.01 µGy/hr

Radiation Exposure Studies Supporting Hormesis

- Radium Dial Painters
- Atomic Bomb Survivors
- Nuclear Shipyard Workers
- Other Nuclear Workers
- Canadian Fluoroscopy Study
- Non-Hodgkin’s Lymphoma Trial
- Taiwan Apartment Dwellers

Radium Dial Painters

- Ingestion of Ra-226 accumulated in bone resulting in chronic high-LET radiation exposure
- 30-year follow-up of 1155 dial painters with total absorbed dose less than 10 Gy showed lower cancer *incidence* than general population and longer life span

Atomic Bomb Survivors

- Life Span Study (LSS) estimated acute plus chronic whole-body exposures
- Cancer *mortality* rate of 7,430 survivors who received 1-19 mGy, less than that of control populations
- Later studies confirm reduced cancer *mortality*, reduced leukemia *mortality* and increased average lifespan of Japanese atomic bomb survivors

Nuclear Shipyard Worker Study

- Two exposed nuclear worker groups
- High-dose (>5 mGy) group *mortality* rate 76% of non-nuclear workers in control group
- Low-dose (<5 mGy) group *mortality* rate 81% of non-nuclear workers in control group

Other Nuclear Worker Study Results

		Control/Exposed		
Study[a]	Dose[b] (mSv)	Population (x 10^3)	Deaths (per 10^3)	Exposed Pop. Deaths as % of Control Pop. Deaths
1	7	21/4	22.0/2.0	9.1
2	20	4.7/3.3	23.7/20.3	85.7
3	66	20.6/15.3	34.8/20.8	59.8
4	25	11.4/2.9	20.5/17.7	86.3

a. 1 – Nuclear Fuel Cycle Workers
   2 – Atomic Energy of Canada Limited Workers
   3 – Hanford/Oak Ridge/Rocky Flats Workers
   4 – Los Alamos Workers (incl. Pu exposure)
b. Estimated lifetime dose per exposed person

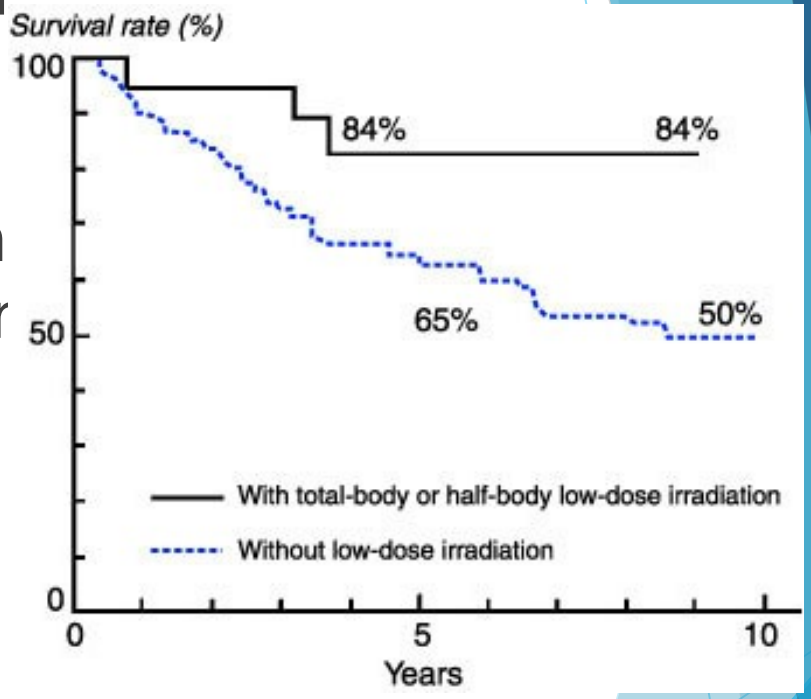
Canadian Fluoroscopy Study

- 1989 study of breast cancer incidence in Canadian women being treated for tuberculosis with high fluoroscopy (x-ray) doses

- Acute exposures <300 mGy showed statistically significant reduction in breast cancer

Non-Hodgkins Lymphoma Trial

- 9-year clinical trial on non-Hodgkin's lymphoma patients
- 23 low-dose radiation patients and 94 contr patients with similar histological tumor grades
- Low-dose radiation group substantially outlived control group at 5 years and 10 years



Taiwan Apartment Dwellers

- Taipei City, Taiwan apartment buildings constructed with Co-60 contaminated materials
- 10,000 apartment dwellers received average collective dose of 400 mGy between 1983 and 2002
- Cancer *mortality* rate and births with congenital heart malformations for apartment dwellers less than for general Taiwan population

Radiation Hormesis Summary

- Concept of radiation hormesis applicable to physiological effects of chronic, low-LET radiation in range of 1 to 50 cGy of total absorbed dose
- Probability of radiation-induced adaptive protection measurably outweighs that of damage from acute doses below 0.2 Gy[4] of low-LET radiation and from chronic dose-rates below 0.08 mGy/hr[32]

Radiation Hormesis Summary (cont.)

- Evidence of hormesis effect of low-dose radiation from numerous radiation exposure studies
- Radiation is poor mutagen and carcinogen
- Low-dose responses seem to be protective and high-dose responses damaging, thus body responds differently to high and low doses

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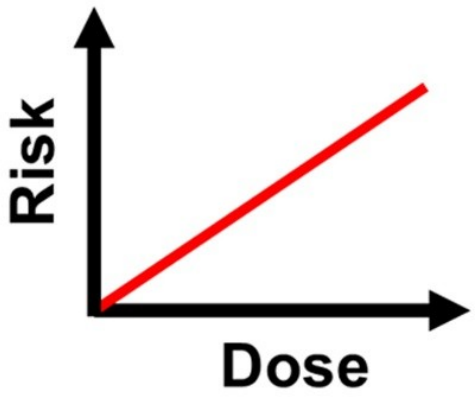
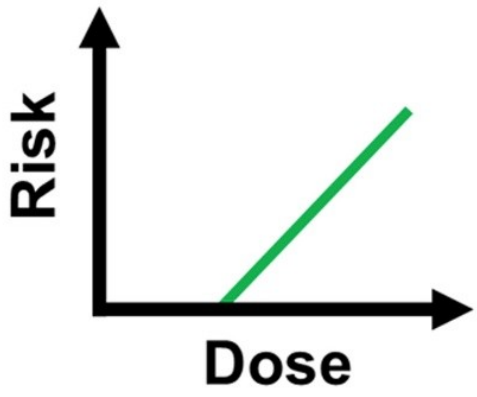
Supplemental Slide

Unscientific LNT model for cancer risk assessment



Modern-science-based threshold model



Unscientific linear no-threshold (LNT) model is the main basis for radiophobia harm. Evolution-associated genomic stress adaptation guarantees a radiation dose threshold for harm.